Amprenavir

Brand Name: Agenerase

Drug Description

Amprenavir is a hydroxyethylamine sulfonamide derivative HIV protease inhibitor (PI). [1]

HIV/AIDS-Related Uses

Amprenavir was approved by the FDA on April 15, 1999, for use in combination with other antiretroviral agents for the treatment of HIV-1 infection.[2] [3] Because of the risk of toxicity from the large amount of propylene glycol in amprenavir oral solution, this dosage form of amprenavir is contraindicated in children under 4 years old, pregnant women, patients with hepatic or renal failure, or patients being treated with disulfiram or metronidazole. Amprenavir oral solution should be used only when amprenavir capsules or other HIV PIs are not therapeutic options.[4]

The amprenavir prodrug fosamprenavir was approved by the FDA on October 20, 2003, for the treatment of HIV infection in combination with other antiretrovirals.[5] Fosamprenavir is rapidly converted to amprenavir in vivo and has a lower pill burden than amprenavir.[6]

Pharmacology

Amprenavir is a selective, competitive, reversible inhibitor of HIV protease, an enzyme that plays an essential role in HIV replication. Amprenavir is pharmacologically related to other HIV PIs but is structurally different from these and other antiretroviral drugs that are currently available. Amprenavir's structure inhibits the function of HIV protease, interfering with the formation of essential viral proteins. The drug is active in both acutely and chronically infected cells; chronically infected cells are not affected by nucleoside reverse transcriptase inhibitors (NRTIs). Although amprenavir does not affect early stages of the HIV replication cycle, it does interfere with the production of infectious HIV, limiting further spread of the virus.

Amprenavir is active against HIV-1 and, to a lesser extent, HIV-2. Unlike nucleoside analogue antiretroviral agents, amprenavir's antiviral activity does not require intracellular conversion to an active metabolite. PIs, including amprenavir, act at a different stage of HIV replication than do NRTIs and nonnucleoside reverse transcriptase inhibitors (NNRTIs). In vitro studies indicate that the antiretroviral effects of HIV PIs and some NRTIs or NNRTIs may be synergistic.[7]

Study results indicate that oral bioavailability of amprenavir is 14% greater when the drug is administered as liquid-filled capsules than when administered as the oral solution. Amprenavir capsules and oral solution are not bioequivalent and are not interchangeable on a mg per mg basis.

When given alone, amprenavir is not well absorbed from the gastrointestinal (GI) tract; however, when formulated with vitamin E, amprenavir's bioavailability substantially increases. In HIV infected adults receiving a 1,200 mg dosage of amprenavir capsules twice daily, peak plasma concentrations averaged 5.36 mcg/ml at 1.9 hours after dosing, and the area under the concentration-time curve (AUC) averaged 18.5 mcg·hour/ml. In HIV infected children 4 to 12 years old who received 5 to 20 mg/kg as liquid-filled capsules, peak plasma concentrations were less than proportional; however, the increases in AUC were proportional. By contrast, HIV infected 4- to 12-year olds receiving 20 mg/kg of oral solution twice daily had an average AUC of 15.46 mcg·hour/ml and peak plasma concentrations of 6.7 mcg/ml at 1.1 hours after dosing. In patients with hepatic impairment, peak plasma concentration may be increased. After receiving a single 600 mg dose of amprenavir, adults with moderate cirrhosis had an average AUC of 25.76 mcg·hour/ml; adults with severe cirrhosis had an average AUC of 38.66 mcg·hour/ml.[8]

Distribution of amprenavir into body tissues has not been fully characterized. The apparent volume of distribution in healthy adults is approximately 430 L. Cerebrospinal fluid concentrations are reportedly less than 1% of plasma concentrations. In vitro, amprenavir is approximately 90% bound to plasma or serum proteins.

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Pharmacology (cont.)

The plasma elimination half-life of amprenavir in HIV infected adults with normal renal and hepatic function ranges from 7.1 to 10.6 hours. The drug is metabolized principally by cytochrome P450 (CYP) isoenzyme 3A4. Less than 3% of amprenavir is eliminated unchanged in urine. After a single oral dose of radiolabled amprenavir, approximately 14% of the dose is eliminated in the urine and 75% in feces, with two metabolites accounting for 90% of radioactivity in feces.[9]

Amprenavir is in FDA Pregnancy Category C.[10] It is not known whether amprenavir crosses the human placenta; however, it does cross the placenta in rats.[11] There are no adequate and well-controlled studies to date using the drug in pregnant women. Amprenavir should be used during pregnancy only when clearly needed. The oral solution form of amprenavir should not be used in pregnant women because the large amount of propylene glycol excipient used in the formulation presents a toxicity risk to the fetus. An Antiretroviral Pregnancy Registry has been established to monitor the outcomes of pregnant women exposed to antiretroviral agents, including amprenavir. Physicians may register patients by calling 800-258-4263 or at the following web site: http://www.APRegistry.com. It is not known whether amprenavir is distributed into human milk; however, it is distributed into milk in rats.[12]

Because amprenavir is metabolized principally by the liver, the manufacturer recommends caution when administering the drug to patients with hepatic impairment.[13]

Strains of HIV-1 with in vitro resistance to amprenavir have emerged during therapy when the drug is given alone or in combination with other antiretroviral agents. The initial mutation following exposure to amprenavir appears to occur at amino acid position 50. This mutation alone generally results in a two- to threefold decrease in susceptibility to the drug.

Clinical evidence suggests that some degree of cross resistance occurs among various HIV PIs. Cross resistance between amprenavir and other PIs has not been fully explored. In initial studies, however, amprenavir and the investigational PI VB-11,328 exhibited a unique resistance pattern that may result in extensive cross resistance between these derivatives but less extensive cross resistance with other PIs. Cross resistance between amprenavir and NRTIs or NNRTIs is unlikely because these drugs have different target enzymes.[14]

Adverse Events/Toxicity

Amprenavir is generally well tolerated. In clinical studies, the most frequently reported side effects have included abdominal pain, diarrhea, hyperglycemia, nausea, oral paresthesia, skin rash, and vomiting. Other reactions include depression or other mood disorders, fatigue, peripheral paresthesia, and taste perversion.[15] [16] [17]

In clinical studies, 22% of patients treated with amprenavir developed skin rash. Although most rashes were of mild to moderate intensity, approximately 1% of patients receiving amprenavir developed a severe or life-threatening rash (Grade 3 or 4), including Stevens-Johnson syndrome. Amprenavir should be discontinued in patients with severe or life-threatening rash or with moderate rash accompanied by systemic reactions.[18]

Body fat accumulation and redistribution, hyperlipidemia, increased bleeding in hemophilia patients, hyperglycemia, exacerbation of existing diabetes mellitus, and new onset diabetes mellitus have been reported in patients receiving PIs, including amprenavir.[19]

Drug and Food Interactions

Amprenavir may be taken with or without food; however, high-fat meals should be avoided because they may decrease the bioavailability of amprenavir. Because both the capsule and oral solution dosage forms of amprenavir contain vitamin E, patients receiving either amprenavir formulation should not take vitamin E supplements. In addition, patients receiving amprenavir oral solution should not consume alcoholic beverages because of the potential risk of adverse effects related to the propylene glycol excipient contained in the oral solution.[20]

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Drug and Food Interactions (cont.)

Although amprenavir appears to be a less potent inhibitor of CYP3A4 than some other PIs, metabolism of amprenavir is mediated by this isoenzyme to some degree. Drugs that induce CYP3A4 may reduce amprenavir plasma concentrations. Conversely, drugs that inhibit this isoenzyme may increase plasma concentrations of amprenavir.[21]

Concomitant use of amprenavir with certain drugs that are highly dependent on CYP3A4 for clearance may raise the plasma levels of these drugs, potentially resulting in serious or life-threatening events. Drugs that are contraindicated with amprenavir include bepridil[22] , dihydroergotamine, ergonovine, ergotamine, methylergonovine, midazolam, pimozide, rifampin, and triazolam. If amprenavir is coadministered with ritonavir, flecainide and propafenone are also contraindicated.[23] For patients receiving amprenavir oral solution, disulfiram is contraindicated.[24]

Amprenavir should not be coadministered with astemizole, cisapride, delavirdine, or terfenadine.[25]

Concomitant use of amprenavir with lovastatin or simvastatin is not recommended. Caution should be used when any HIV PIs, including amprenavir, are used concurrently with other HMG-CoA reductase inhibitors that are metabolized by the CYP3A4 pathway (for example, atorvastatin or cerivastatin). The resulting increased concentration of statins may increase the risk of myopathy or rhabdomyolysis.

Concomitant use of products containing St. John's wort (Hypericum perforatum) with amprenavir or other PIs is not recommended. St. John's wort is expected to substantially decrease drug plasma levels and may lead to loss of virologic response and possible resistance to amprenavir or other PIs.

Serious or life-threatening events can occur if amprenavir is taken with amiodarone, lidocaine, tricyclic antidepressants, and quinidine. Patients receiving amprenavir concomitantly with any of these drugs should be carefully monitored.

Caution should be used when prescribing sildenafil in patients receiving PIs, including amprenavir. Coadministration of a PI with sildenafil is expected to substantially increase sildenafil concentrations and, possibly, sildenafil-associated adverse effects, including hypotension, visual changes, and priapism.

Concomitant use of amprenavir with certain other drugs may significantly increase or decrease plasma concentrations of amprenavir or of the coadministered drug. Adjustment in dosage or regimen should be considered when amprenavir is coadministered with any of the following drugs: antacids, atorvastatin, didanosine, ketoconazole, itraconazole, methadone, rifabutin, and ritonavir.

Concomitant use of amprenavir and oral or other contraceptives containing ethinyl estradiol/norethindrone may lead to loss of virologic response. Alternative methods of nonhormonal contraception are recommended.[26]

Amprenavir is a sulfonamide. The potential for cross-sensitivity between other sulfonamides and amprenavir is unknown. Amprenavir should be used with caution in patients with a known sulfonamide allergy.[27]

Contraindications

Amprenavir is contraindicated in patients with clinically significant hypersensitivity to the drug or any components in either of the formulations.[28] Because of potential toxicity from the large amount of propylene glycol excipient in amprenavir oral solution, this dosage form is contraindicated in children under 4 years old, pregnant women, patients with hepatic or renal failure, and patients being treated with disulfiram or metronidazole.[29]

Clinical Trials

For information on clinical trials that involve Amprenavir, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Amprenavir AND HIV Infections.

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Dosing Information

Mode of Delivery: Oral.[30]

Dosage Form: 50 mg or 150 mg liquid-filled capsules and 15 mg amprenavir per ml oral solution.

Capsules: The recommended dose is 1,200 mg (eight 150 mg capsules) twice daily. If amprenavir and ritonavir are used in combination, the recommended dosage regimens are as follows: amprenavir 1,200 mg with ritonavir 200 mg once daily or amprenavir 600 mg with ritonavir 100 mg twice daily. For adolescents age 13 to 16 years, the recommended dose is 1,200 mg (eight 150 mg capsules) twice daily in combination. For patients age 4 to 12 years or for patients age 13 to 16 years weighing less than 50 kg (66 lbs), the recommended dose is 20 mg/kg twice daily or 15 mg/kg three times daily (to a maximum daily dose of 2,400 mg). Amprenavir capsules should be used with caution in patients with moderate or severe hepatic impairment. Patients with a Child-Pugh score ranging from 5 to 8 should receive a reduced dose of 450 mg twice daily, and patients with a Child-Pugh score ranging from 9 to 12 should receive a reduced dose of 300 mg twice daily.[31]

Oral solution: The recommended dose for adults, adolescents age 16 and older, and adolescents age 13 to 16 who weigh more than 50 kg is 1,400 mg twice daily. For children age 4 to 12 or adolescents age 13 to 16 who weigh less than 50 kg, the recommended dose is 22.5 mg/kg twice daily (maximum dose 2,800 mg per day) or 17 mg/kg three times a day (maximum dose 2,800 mg per day).[32]

Storage: Liquid-filled capsules and oral solution should be stored at controlled room temperature of 25 C (77 F).[33]

Chemistry

CAS Name: (3S)-tetrahydro-3-furyl N-[(1S,2R)-3-(4-amino-N-isobutylbenzenesulfonamido)-1-benzyl-2-hydroxypropl]carbamate[34]

CAS Number: 161814-49-9[35]

Molecular formula: C25-H35-N3-O6-S[36]

C59.39%, H6.98%, N8.31%, O18.98%, S6.34%.[37]

Molecular weight: 505.64[38]

Physical Description: White to cream-colored solid.[39]

Stability: When stored as directed, the capsules have an expiration date of 1.5 years and the oral solution has an expiration date of 1 year after manufacture.[40]

Solubility: Solubility of 0.04 mg/ml in water and 86 mg/ml in alcohol.[41]

Other Names

141W94[42]

Tetrahydro-3-furyl N-(3-(4-amino-N-isobutylbenzenesulfonamido)-1-benzyl-2-hydroxypropyl)carbamate[43]

Vertex VX478[44]

VX-478[45]

APV[46]

Further Reading

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Manufacturer Information

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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help

Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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